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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,570	11/07/2005	James E Mullally	007180-69 US	4192

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EXAMINER	
PAGONAKIS, ANNA	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,570	MULLALLY, JAMES E	
	Examiner	Art Unit	
	ANNA PAGONAKIS	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments filed 6/22/2009 have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making compounds of the generic formula of instant claim 9 and for using the compound of page 8 of the instant specification, does not reasonably provide enablement for using the full scope of compounds instantly claimed (claim 1). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The presently claimed invention is directed to a pharmaceutical composition a compound having an alpha,beta,-unsaturated ketone, wherein said ketone has a sterically inaccessible electrophilic beta-carbon. The presently claimed invention is further directed to a pharmaceutical composition comprising a alpha,beta,-unsaturated ketone, wherein said ketone has a sterically inaccessible electrophilic beta-carbon.

In particular, one skilled in the relevant art could not practice the presently claimed subject matter without undue experimentation because the skilled artisan would not have accepted on its face that the breadth and variation of chemical compounds that are encompassed by the claimed genera would necessarily have the same or substantially similar efficacy in achieving the disclosed utilities, [e.g., inhibition of ubiquitin isopeptidase], as the compound of Example 1 studied in the instant specification as being representative of the claimed genera.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112 *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support*; assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

Applicant is also reminded of MPEP §2164.08, which directs that all questions of enablement must be evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the

art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involves the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

The present rejection is not based exclusively on the breadth of the claims. Rather, the rejection is based upon the fact that Applicant has not provided adequate enabling direction as to how to use the entire scope of compounds instantly claimed, since the specification is primarily directed to the use of the compounds of page 8 of the instant specification a representative species of the claimed genus and provides no evidentiary basis (or even scientific rationale) for extrapolating the results seen with the compounds of page 8 of the instant specification to the much larger and highly varied genus of compounds presently claimed. Accordingly, the claims read upon a genus with a single common structural element but encompasses compounds with substantial structural, chemical and, therefore, functional variation. Claim breadth alone is not a sufficient basis for concluding a lack of enabling direction; however, where the claims encompass such a large and variable genus of compounds, where only one has been exemplified as being useful for the disclosed utilities, and the state of the art is sufficiently unpredictable such that one of ordinary skill in the art would have been skeptical to extrapolate the efficacy seen with a single species to this larger and more highly varied genus of compounds, a conclusion of a lack of enabling direction is appropriate.

Applicant's claims encompass compounds with at least the basic core structure as set forth in instant claim `, which allows for thousands, if not millions, of permutations of this physical structure due to the number of possible moieties that may be attached to this basic structure. Such substitutions give rise to an enormous number of compounds that are substantially different in physical and chemical structure such that the efficacy demonstrated with a few species (i.e., the compounds of page 8 of the

instant specification) would not necessarily be representative of such a vast and variable genus of compounds, depending on the substitution(s) present in the molecule.

It was known in the art at the time of the present invention that even compounds that share similar structural properties cannot be guaranteed to have the same level of activity. Such is the unpredictable nature of the pharmaceutical arts, as acknowledged by Remington's Pharmaceutical Sciences, which states, "Two-dimensional structural organic formulas are very poor means of representing the physical, chemical or biologic properties of a molecule. Structural formulas merely depict the way the various atoms are strung together to form what is known as a *molecule*. Drugs that are strikingly similar in structure may demonstrate widely differing pharmacologic properties, while two drugs of apparently different structure can exhibit almost identical activity. Reference to Table I [see pages 421-424] easily confirms these facts. There are many factors other than simple structural variation that have an effect on the activity of a drug." (see first paragraph, column 1, page 425) Such factors include, but are not limited to, molecular size, shape, ionization, charge distribution, solubility, interatomic distance, geometric and stereochemical configurations, and the rigidity or flexibility of the molecule (see pages 425-426).

This well-recognized unpredictability in the art must be taken into consideration when determining whether a disclosure fails to provide sufficient enabling direction for the claimed subject matter. As directed by the MPEP, the amount of guidance required to be present in the specification as originally filed is directly proportional to the amount of knowledge in the art as well as the unpredictability in the art. In other words, if little or nothing is known in the prior art about an aspect of the claimed invention and the art is unpredictable, the specification needs more detail and guidance as to how to use the invention in order to be enabling. Please reference *In re Fisher*, 417 F.2d 833, 839, 166 USPQ 18, 23 (CCPA 1970) and *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

Applicant's exemplification of the species of page 8 of the instant specification does not address

the variability in physical and chemical structure of the claimed genera of compounds such that one of ordinary skill in the art would have been imbued with the reasonable expectation of success in effectively employing any one or more of such compounds (aside from the specific species of page 8 of the instant specification) for any one or more of the disclosed utilities. In fact, the variability in physical and chemical structure of the compounds encompassed by Applicant's claimed genus precludes the extrapolation of the exemplified results of the compounds of page 8 of the instant specification to this larger and much more highly varied genus of compounds of the generic formula instantly claimed, absent any criteria or scientific or evidentiary basis upon which to rely. As a result, the skilled artisan would not be able to readily determine what other compounds within the scope of those intended by Applicant would reasonably have possessed a therapeutic effect in achieving any one or more of the disclosed utilities in the absence of such evidence or guidance by the specification. In other words, the skilled artisan would have no alternative recourse but the undue burden of experimentation in order to determine those other compounds of the genera claimed that could be used, with a reasonable expectation of success, for the presently described utilities.

It is well settled in patent law that in cases involving chemicals and chemical compounds, which differ radically in their properties, it must appear in an Applicant's specification either by enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result. Though Applicant's exemplification of the compounds of page 8 of the instant specification has been noted, this single working example is not sufficiently representative of the thousands, if not millions, of compounds presently claimed. The exemplification of the few compounds of page 8 of the instant specification, while enabling in and of itself, fails to provide basis for enabling the entire vast scope of compounds presently claimed without any evidence or reasoning by Applicant addressing the unpredictability in the pharmaceutical and medical arts and how this single example is representative of the claimed genus as a

whole. While the lack of multiple working embodiments cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the art and the limited direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

It is noted that Applicant is not required to enable each and every single embodiment encompassed by the claims. While the scope of the required enablement varies inversely with the degree of unpredictability involved, even in the unpredictable arts, such as pharmaceuticals and medicine, a disclosure of every operable species is not required. However, while a single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements, [please see *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971)], in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. Please reference *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. Please reference *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947, F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species what other species will work. Please see MPEP §2164.03. In the absence of additional disclosure, the skilled artisan would be required to perform an undue level of experimentation in order to determine the other species that would be capable of performing the disclosed utilities.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this

particular art is not at all uncommon, but that the experimentation required in order to practice this aspect of the invention would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation or ability to use the full scope of the invention as instantly claimed, given the disclosure and supporting examples provided in the present specification and the state of the art at the time of the invention. In order to actually achieve the claimed invention, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the embodiments presently claimed.

Response to Applicant's Remarks

Applicant alleges that the instant specification provides sufficient examples and guidance related to the use of compounds having an alpha,beta-unsaturated ketone with a sterically accessible electrophilic-beta carbon that are not cyclopentenane prostaglandins of the J family. This is not found persuasive. Firstly, Applicant has not provided any guidance as to where in the instant disclosure such examples are found. Further, a careful review of the disclosure again reveals that only a limited number of punaglandins were tested (see page 33 of instant disclosure).

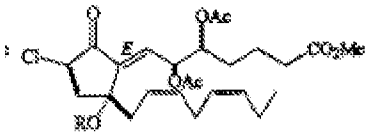
Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Baker et al (Journal of Natural Products, 1994).

Baker et al teach of the elected compound (page 1347):



5 R=H

where the compound was administered to L1210 mouse leukemia cells (page 1349, lines 5-6).

The explanation of an effect obtained when contacting the cell with the elected compound cannot confer novelty on a known process. In other words, even if the inhibition of ubiquitin isopeptidase was not itself recognized as a pharmacological effect of contacting the elected compound to cells, such an effect is not considered a new therapeutic application since the very contact of the cells with the elected compound, which is well known in the prior art, would also inhibit ubiquitin isopeptidase. Though new properties of a compound are no doubt important contributions to scientific and pharmacological development, the assessment of patentability is not based on the mechanisms or properties by which they exert a therapeutic effect. Contacting the cells with the same compound described in the specification described as an inhibitor of ubiquitin isopeptidase, necessarily provides for the claimed activity. In other words, the method step of contacting the leukemia cells with the elected compound, inherently performs the function of inhibiting of ubiquitin isopeptidase.

Response to Applicant's Remarks

Applicant alleges that Baker merely mentions that two of the nineteen marine coral punaglandins that were investigated had an effect in an investigatory leukemia cell line and that Baker provide no basis for believe that there is consisting inhibition of ubiquitin isopeptidase. This is not found persuasive. Firstly, it is noted that Applicant has not addressed the anticipation rejection set forth. Though mechanisms of action of chemical entities are no doubt important contributions to scientific and pharmaceutical development, the assessment of patentability under 35 U.S.C. 102 is based upon the therapeutic applications and effects of the compounds, not the mechanisms by which they exert such a therapeutic effect. Furthermore, it is generally well settled in the courts that a mechanistic property of a chemical compound, when administered under identical conditions, is necessarily present, despite the fact that it may not have been readily apparent to, or recognized by, one of ordinary skill in the art.

Conclusion

No claim is found to be allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNA PAGONAKIS whose telephone number is (571)270-3505. The examiner can normally be reached on Monday thru Thursday, 9am to 5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AP

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614